

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) An assembly comprising:

a plane substrate having a first surface part and an opposite second surface part, the first surface part having a plurality of sites in the first surface part of the substrate each of which is adapted to hold an ion channel-containing structure contained in a liquid, and each of which has a passage therein through the substrate connecting the first surface part and the second surface part, which passage has walls and is dimensioned to hold an ion channel-containing structure and to form a high resistance seal between said ion channel-containing structure and said substrate around, or along the walls of said passage,

a plurality of measuring electrodes, each of which is associated with a respective site,

one or more reference electrodes, the measuring electrodes and the respective reference electrode or reference electrodes being electrodes capable of passing, when in electrolytic contact with each other and when a potential difference is applied between them, a current between them by delivery of ions by one electrode and receipt of ions by the other electrode,

each of the sites being adapted to provide a high electrical resistance seal established between an area of contact of an outer surface of [[the]] an ion channel-containing structure held at the site, and [[a]] the first surface part of the substrate around, or along the walls of said passage, the seal, when established, separating a domain defined on one side of the seal established by the ion channel-containing structure and in electrolytic contact with the measuring electrode, from a domain defined on the opposite side of the seal established by the ion channel-containing structure and in electrolytic contact with the respective reference electrode, whereby a current flowing between the reference and respective measuring electrodes and through the ion channel-containing structure can be determined and/or monitored,

the electrodes being integrated with the assembly, wherein the assembly further comprises a plurality of flow channel structures created in the substrate for delivering liquid to said plurality of sites.

2. (Original) An assembly according to Claim 1 wherein the plane substrate has a first side and a second side, the first and second sides being spaced apart from one another and defining a first substrate thickness, the first surface part and the opposite second surface part being spaced apart from one another and defining a second substrate thickness, the second substrate thickness being less than the first substrate thickness.

3. (Currently Amended) An assembly as claimed in Claim 2 wherein the plane substrate comprises a first substrate component, and a second substrate component, the first substrate component having a first face forming the first side of the plane substrate, and an opposite, second face, and the second substrate component having a first face defining the second side of the plane substrate, and an opposite, second face, the first and second substrate components being attached to one another at their respective second faces.

4. (Original) An assembly according to Claim 2 or Claim 3 wherein the plurality of flow channel structures is formed in the first side of the plane substrate.

5. (Original) The assembly according to Claim 1, wherein the substrate is a silicon substrate, and the surface part of the site with which the high electrical resistance seal is to be established is a silica surface part.

6. (Original) The assembly according to Claim 1 or 2, wherein the plurality of sites is arranged in an array on the first surface part of the substrate.

7. (Original) The assembly according to Claim 6, wherein the array of sites comprises at least 9 sites.

8. (Original) The assembly according to Claim 1, wherein the measuring and reference electrodes are silver/silver halide electrodes.

9. (Original) The assembly according to Claim 8, wherein the measuring and reference electrodes are silver/silver chloride electrodes.

10. (Original) The assembly according to Claim 1 or Claim 2, comprising a first layer of hydrophobic material positioned on or above the surface of the substrate, said first layer covering only parts of the surface of the substrate.

11. (Original) The assembly according to Claim 10, where one or more sites are located within parts of the surface of the substrate not covered by said first layer.

12. (Original) The assembly according to Claim 1 or Claim 2, comprising one or more wells extending into the substrate and having well openings defined in the first surface part, each having a bottom part and a side part, at least some of the sites of the first surface part being positioned within the bottom parts of the wells such that a well and a passage together define a funnel.

13. (Original) The assembly according to Claim 12, wherein the plurality of flow channel structures enable liquid to be added to the one or more funnels.

14. (Original) The assembly according to Claim 13, wherein the plurality of flow channel structures comprises an inflow and an outflow port to/from the one or more funnels.

15. (Original) The assembly according to Claim 12, wherein the wells have been formed by a process comprising a photolithography/etching process.

16. (Original) The assembly according to Claim 15, wherein the substrate is a silicon substrate, and wherein the wells are shaped as truncated pyramids the bottoms of which are constituted by the well openings, and the side parts of which have a slope of 54.7°.

17. (Currently Amended) The assembly according to ~~any of Claims 12 to 16~~ Claim 12, wherein a reference electrode is positioned on the side part of each well.

18. (Original) The assembly according to Claim 1 or Claim 2, wherein the measuring electrode associated with each site is positioned at each respective site.

19. (Original) The assembly according to Claim 1, wherein the transverse dimension of the passage is 1-5 μ m.

20. (Original) The assembly according to Claim 2, wherein the measuring electrode associated with each site is positioned on the opposite second surface part of the substrate.

21. (Original) The assembly according to Claim 20, wherein the measuring electrode associated with each site is positioned adjacent to an opening of the passage defined at the respective site.

22. (Original) The assembly according to Claim 1 or Claim 2, further comprising, for each of the sites, an electronic circuit that is connected with the respective measuring electrode and with the reference electrode or one of the reference electrodes for generation of an amplified signal that is a unique function of a current flowing through ion channels between said electrodes.

23. (Currently Amended) An assembly according to ~~any one of the preceding claims~~ claim 1 further comprising a connection means for connecting the substrate to a suction means for creating a suction on said ion channel-containing structure and through said passage so as to enable the ion channel-containing structure to be positioned, sealed and ruptured by the suction, wherein, in use

the first surface part is in contact with the liquid containing the ion channel containing structure, the connection means forming an integral part of the assembly and extending from the second surface part of the substrate to the first side of the substrate.

24. (Currently Amended) A method of establishing a whole cell measuring configuration for determining and/or monitoring an electrophysiological property of one or more ion channels of one or more ion channel-containing structures, said method comprising the steps of:

providing an assembly comprising: a plane substrate having a first surface part and an opposite second surface, said substrate having a plurality of sites in the first surface part of the substrate, each of which is adapted to hold an ion channel-containing structure and each of which has a passage therein through the substrate connecting the first surface part and the second surface part, which passage has walls and is dimensioned to hold an ion channel-containing structure and to form a high resistance seal between said ion channel-containing structure and said substrate, around or along the walls of said passage, a plurality of measuring electrodes, each of which is associated with a respective site, and one or more reference electrodes;

supplying a carrier liquid at one or more sites using a plurality of flow channel structures created in the substrate, said carrier liquid containing one or more ion channel-containing structures the carrier liquid contacting the first surface part of the substrate;

positioning at least one of the ion channel-containing structures at a corresponding number of sites;

forming a high electrical resistance seal between an area of contact of the outer surface of an ion channel-containing structure held at the site and a first surface part of the substrate around or along the walls of said passage, the seal, when established, separating a domain defined on one side of the seal established by the ion channel-containing structure and in electrolytic contact with the measuring electrode from a domain defined on the opposite side of the seal established by the ion channel-containing structure and in electrolytic contact with the respective reference electrode;

checking for a high electrical resistance seal between an ion channel-containing structure held at a site and the first surface part of the substrate or along the walls of said passage with which the high electrical resistance seal is to be established by successively applying a first electric potential difference between the measuring electrode associated with the site and a reference electrode, monitoring a first current flowing between said measuring electrode and said reference electrode, and comparing said first current to a predetermined threshold current and, if the first current is at most the predetermined threshold current, then approving the site as having an acceptable seal between the ion channel-containing structure and the first surface part of the site; and

establishing a whole-cell configuration at approved sites,

whereby a third current flowing through ion channels of the ion channel-containing structure between the measuring electrode and the reference electrodes can be determined and/or monitored.

25. (Original) A method according to Claim 24 wherein the substrate comprises a first side and second side spaced apart from the first side, the first and second sides defining a first substrate thickness, and the first and second surface parts of the substrate defined in the second substrate thickness, the second substrate thickness being less than the first substrate thickness.

26. (Original) A method according to Claim 25, wherein the substrate is formed from a first substrate component and a second substrate component, the first substrate component having a first face formed from the first side of the plane substrate, and an opposite face, the second substrate having a first face defining the second side of the plane substrate, and an opposite, second face, the first and second substrate components being attached to one another at their respective second faces.

27. (Original) A method according to Claim 25 or 26, wherein the flow channel structures are formed on the first side of the plane substrate.

28. (Currently Amended) A method according to ~~Claims 24 to 27~~ Claim 24, wherein the step of establishing a whole-cell configuration at approved sites comprises applying, between the measuring electrode associated with each approved site and a reference electrode, a series of second electric potential difference pulses, monitoring a second current flowing between the measuring electrode and the reference electrode, and interrupting the series of second electric potential difference pulses whenever said second current exceeds a predetermined threshold value, thereby rupturing a part of the ion channel-containing structure.

29. (Currently Amended) A method according to ~~any one of Claims 24 to 28~~ Claim 24 wherein the assembly further comprises connection means for connecting the substrate to a suction means, the connecting means extending from the second surface part to the first side of the substrate, and the step of establishing a whole cell configuration at approved sites comprises forming the high electrical resistance seal between an area of contact of the outer surface of an ion channel-containing structure held at the site and a first part of the substrate around or along the walls of said passage being formed by applying a suction to said passage via said connection means.

30. (Currently Amended) The method according to ~~Claims 24 to 29~~ Claim 24, wherein the step of establishing a whole-cell configuration at approved sites comprises subjecting a part of the ion channel-containing structure with a pore forming substance.